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# Outcome Differences between Intra-Arterial Iso- and Low-Osmolality Iodinated Radiographic Contrast Media in the Interventional Management of Stroke III Trial

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## ABSTRACT

**BACKGROUND AND PURPOSE:** Intracarotid arterial infusion of nonionic, low-osmolal iohexol contrast medium has been associated with increased intracranial hemorrhage in a rat middle cerebral artery occlusion model compared with saline infusion. Iso-osmolal iodixanol (290 mOsm/kg H<sub>2</sub>O) infusion demonstrated smaller infarcts and less intracranial hemorrhage compared with low-osmolal iopamidol and saline. No studies comparing iodinated radiographic contrast media in human stroke have been performed, to our knowledge. We hypothesized that low-osmolal contrast media may be associated with worse outcomes compared with iodixanol in the Interventional Management of Stroke III Trial (IMS III).

**MATERIALS AND METHODS:** We reviewed prospective iodinated radiographic contrast media data for 133 M1 occlusions treated with endovascular therapy. We compared 5 prespecified efficacy and safety end points (mRS 0–2 outcome, modified TIC1 2b-3 reperfusion, asymptomatic and symptomatic intracranial hemorrhage, and mortality) between those receiving iodixanol (*n* = 31) or low-osmolal contrast media (*n* = 102). Variables imbalanced between iodinated radiographic contrast media types or associated with outcome were considered potential covariates for the adjusted models. In addition to the iodinated radiographic contrast media type, final covariates were those selected by using the stepwise method in a logistic regression model. Adjusted relative risks were then estimated by using a log-link regression model.

**RESULTS:** Of baseline or endovascular therapy variables potentially linked to outcome, prior antiplatelet agent use was more common and microcatheter iodinated radiographic contrast media injections were fewer with iodixanol. Relative risk point estimates are in favor of iodixanol for the 5 prespecified end points with M1 occlusion. The percentage of risk differences are numerically greater for microcatheter injections with iodixanol.

**CONCLUSIONS:** While data favoring the use of iso-osmolal iodixanol for reperfusion of M1 occlusion following IV rtPA are inconclusive, potential pathophysiologic mechanisms suggesting clinical benefit warrant further investigation.

**ABBREVIATIONS:** EVT = endovascular therapy; IA = intra-arterial; ICH = intracranial hemorrhage; IMS III = Interventional Management of Stroke III Trial; IRCM = iodinated radiographic contrast media; LOCM = low-osmolal contrast media; MCI = microcatheter injection; mTICI = modified TIC1; SICH = symptomatic intracranial hemorrhage

Iodinated radiographic contrast media (IRCM) have variable antithrombotic, fibrinolytic, cytotoxic, hydrostatic, and vasoactive effects. In a rat middle cerebral artery reperfusion model, intracarotid arterial infusion of the nonionic low-osmolal con-

trast medium (LOCM) iohexol (672 mOsm/kg, H<sub>2</sub>O) increased intracerebral hemorrhage (ICH) compared with saline infusion.<sup>1</sup> Iso-osmolal iodixanol (290 mOsm/kg H<sub>2</sub>O) infusion led to

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From the Department of Radiology (T.A.T., J.C., H.M.), University of Cincinnati Academic Health Center, University Hospital, Cincinnati, Ohio; Department of Public Health Sciences (L.D.F., Y.Y.P., S.D.Y.), Medical University of South Carolina, Charleston, South Carolina; University of California, Los Angeles Stroke Center (D.S.L.), Los Angeles, California; Department of Radiology and Clinical Neurosciences (M.D.H., M.G.) and Calgary Stroke Program (A.M.D.), Department of Clinical Neurosciences/Medicine/Community Health Sciences, Hotchkiss Brain Institute, University of Calgary, Calgary, Alberta, Canada; Departments of Neuroradiology (R.v.K.) and Neurology (V.P.), Dresden University Stroke Center, Universitätsklinikum Carl Gustav Carus Technische Universität Dresden, Dresden, Germany; Department of Neurology (I.D.), Elblandklinikum Meissen, Academic Teaching Hospital of Universitätsklinikum, Carl Gustav Carus Technische Universität Dresden,

Meißen, Germany; Department of Neurology (J.B., P.K.), University of Cincinnati Academic Health Center, Cincinnati, Ohio; and The Stroke Institute (T.J.), University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania.

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Please address correspondence to Thomas A. Tomsick, MD, University of Cincinnati Academic Health Center, UC Health, Department of Radiology, 234 Goodman St, Cincinnati, OH 45267-0761; e-mail: thomas.tomsick@uchealth.com

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**Table 1: Baseline clinical characteristics considered for adjusted analysis**

	Iodixanol	LOCM <sup>a</sup>	P Value
Age <sup>b</sup> (median) (range) (yr)	73 (47–83)	68.5 (24–82)	.07
Baseline glucose <sup>b</sup> (mmol/L) (median) (range)	6.9 (5.2–18.3)	6.6 (3.8–21.5)	.33
Diabetes (%)	19.4	17.7	.83
Baseline SBP (mm Hg) <sup>b</sup> (median) (range)	145.5 (116–185)	146 (102–194)	.82
History of high BP (%)	74.2	73.5	.94
Atrial fibrillation (%)	48.4	35.3	.19
Coronary artery disease (%)	35.5	19.6	.07
ASPECTS 8–10 <sup>b</sup> (%)	41.9	49.0	.49
Baseline NIHSS <sup>b</sup>			
≥20%	35.5	37.3	.86
≤19%	64.5	62.8	
Historical mRS (No. Sx) <sup>b</sup> (%)	90.3	86.3	.46
Antiplatelet agents (%)	67.7	44.1	.02
Presumptive stroke location right (%)	51.6	49.0	.80
Baseline CTA/MRA (%)	61.3	51.0	.31

**Note:**—Sx indicates symptoms; SBP, systolic blood pressure; BP, blood pressure.

<sup>a</sup> Four LOCM (mOsm/Kg H<sub>2</sub>O): iohexol (672), iopamidol (616), ioversol (651), iopromide (607).<sup>11</sup>

<sup>b</sup> Baseline factors relevant to prespecified outcomes.

smaller infarcts and less ICH compared with both low-osmolal iopamidol and saline in a similar model.<sup>2</sup> Dzialowski et al<sup>3</sup> reported reduced odds of favorable outcome in patients receiving intravenous IRCM for CT angiography before IV thrombolysis.

Practical differences exist as well: IRCM differ in cost (ie, iodixanol is more expensive than LOCM) and ease of use (ie, iodixanol is more viscous and more difficult to inject). No study has prospectively and comprehensively compared outcomes according to intra-arterial (IA) IRCM use in endovascular therapy (EVT) of ischemic stroke in humans, to our knowledge. We report the efficacy and safety outcomes for subjects with EVT for MCA M1 occlusion in the Interventional Management of Stroke III Trial (IMS III) according to IRCM type and osmolality.

## MATERIALS AND METHODS

Study eligibility/exclusion criteria, methods, and results have been previously reported.<sup>4,5</sup> Six hundred fifty-six subjects were randomized to either IV rtPA or IV rtPA plus endovascular therapy. CT angiography or MR angiography was not required but was allowed in centers where either was established as a local standard of evaluation and care. Five EVT methods were approved for use during the course of the trial (thrombolysis via standard microcatheter/guidewire rtPA infusion or the EkoSonic Endovascular System [EKOS, Bothell, Washington])<sup>6</sup>; clot removal via the Merci system (Concentric Medical, Mountain View, California),<sup>7,8</sup> Penumbra System (Penumbra, Alameda, California),<sup>9</sup> or Solitaire FR Retriever (Covidien, Irvine, California).<sup>10</sup> Intra-arterial rtPA infusion was also allowed as an adjuvant to mechanical thrombectomy. A 2000-U bolus of heparin was required per protocol for endovascular treatment procedures, followed by 500-U/h IV infusion.

The primary outcome measure was a modified Rankin Scale score of 0–2 at 90 days. Secondary EVT efficacy end points included revascularization, as measured by Modified Thrombolysis in Cerebral Infarction (mTICI) 2–3 and mTICI 2b–3 as ascribed by consensus of the Angiography Core Laboratory members (T.A.T., D.S.L.). Primary safety end points were 90-day mortality and symptomatic intracranial hemorrhage (SICH) within 30 hours of IV rtPA initiation, defined as an ICH temporally related to a decline in neu-

rologic status and new or worsening neurologic symptoms in the judgment of the clinical investigator that may warrant medical intervention. Asymptomatic ICH within 30 hours of IV rtPA initiation was a secondary safety end point.

Investigators prospectively entered data on the IRCM compound type and volume for EVT subjects. The percentage of iodine concentration and/or specific IRCM osmolality was not consistently recorded. Clinical efficacy and safety end points were analyzed for subjects with EVT for M1 occlusion (defined as occlusion of the MCA trunk with 100% MCA distribution at risk, exclusive of a typical anterior temporal artery distribution), according to EVT use of either iso-

osmolal iodixanol or any LOCM.

The 2 IRCM groups were initially compared for differences in prescribed outcomes that might warrant further comparative analysis. Baseline risk factors with a potential effect on clinical efficacy or safety outcome in revascularization therapy were then compared for balance between the 2 groups. Baseline variables imbalanced between IRCM types or associated with outcome ( $P < .1$ ) were considered potential covariates for the adjusted models. Imbalance/association was measured by using the  $\chi^2$ , Fisher, or Wilcoxon 2-sample test, as appropriate. The linearity in the logit assumption was checked for all continuous potential covariates. In addition to IRCM type, final covariates were those selected by using the stepwise method in a logistic regression model. Model fit was assessed via the Hosmer-Lemeshow test. For ease of interpretation, adjusted relative risks were then estimated by using a log-link regression model.

## RESULTS

Thirty-one M1 occlusions were treated with iodixanol use during EVT, and 102, with LOCM of 4 different types. Differences in baseline characteristics known to be relevant in stroke efficacy or safety outcome with revascularization therapy and other relevant treatment-related variables are included in Tables 1 and 2.

Table 3 details relative and absolute efficacy and safety differences between the 2 IRCM groups.

Separate adjusted models were fit for each outcome (except SICH, due to an insufficient event rate). Variables imbalanced between IRCM types or associated with outcome ( $P < .1$ ) were considered potential covariates for the adjusted models, including antiplatelet medication (67.7% iodixanol versus 44.1%,  $P = .0212$ ), history of coronary artery disease (35.5% iodixanol versus 19.6%,  $P = .0671$ ), age (iodixanol median, 73 versus 68.5 years,  $P = .0698$ ), and microcatheter injection (MCI) (median, 1 iodixanol versus 2 LOCM;  $P = .03$ ), varied according to IRCM type.

Adjusted relative risk point estimates were in favor of the iodixanol group for all outcomes (Table 4). No significant differences for specified outcomes were identified. Conclusions remained the same after sensitivity analyses were performed for asymptomatic ICH and

mRS 0–2 outcome models to include adjustments for variables known to be associated with these outcomes.

As a known variable affecting procedure outcome that was unequally distributed, MCIs were further analyzed. In bivariate analysis of MCI number compared with outcomes independent of the IRCM group, significant relationships were identified. Fewer MCIs were associated with greater mRS 0–2 outcome ( $P = .029$ ) and better reperfusion ( $P = .003$ ). MCI remained a significant predictor of reperfusion when adjusted for key baseline and treatment-related variables. MCIs were not significant predictors of mRS 0–2 or mortality when adjusted for other key variables. Ninety-one of 133 (68.5%) subjects had MCIs, including 16/31 (52%) with iodixanol and 75/102 (73.5%) with LOCM ( $P = .022$ ). With MCI use, percentage risk differences in the measured end points were in favor of iodixanol for all end points. MCI use did not differ among device methods.

## DISCUSSION

The potential risks and safety of IRCM use in the setting of acute stroke in humans have been discussed for a long time, with the advantages in diagnosis and treatment assumed to outweigh any theoretic, unproven risks.<sup>11,12</sup> However, with effective ischemic stroke therapies now available, investigation and deeper understanding of the theoretic effects of different media may assume greater practical significance.

Our analyses here disclose potential differences in outcomes from stroke treatment arising from the use of IA iso-

osmolal iodixanol versus LOCM agents for EVT following IV rtPA in the setting of microcatheter use. Raw, unadjusted, and adjusted directions of effect were in favor of iodixanol for all prespecified efficacy and safety outcomes. Relatively greater age, blood glucose, percentage of atrial fibrillation, and CT hypoattenuation (as manifested by a lower ASPECT score), followed by relatively later IV rtPA administration, longer time to artery puncture, and more thrombolysis-only procedures, were present in the iodixanol group. Prior antiplatelet use, the only baseline variable significantly greater with iodixanol, has been associated with a small excess of SICH in systemic thrombolytic therapy.<sup>13</sup> While these factors should disadvantage iodixanol regarding mRS 0–2 outcome and ICH rate, point estimates from adjusted analyses remain in favor of iodixanol. MCIs were less common in the iodixanol group. Procedures with no MCI showed no benefit to iodixanol use. When MCIs were analyzed according to IRCM use, however, a greater relative benefit was suggested with MCI iodixanol use compared with LOCM for all end points.

IRCM effects may be collectively related to their ionic or non-ionic properties, iso-osmolality, and their molecular structure and size as monomers or dimers. Osmolality is, in part, related to iodine concentration, generally recommended at 300-mg per cent for cerebral use. Multiple iodine concentrations of the same IRCM compound type were used in IMS III. Consensus that the use of ionic high-osmolal IRCM was associated with worse outcome after infarction in humans and animals has eliminated their use in this setting.<sup>11,12,14</sup> LOCM non-ionic media may contribute to ICH in animals.<sup>1</sup> Differences in ICH number and infarct area effects might also exist between injection of iso-osmolal and LOCM.<sup>2</sup> It is reasonable to further hypothesize, then, that nonionic iso-osmolal IRCM may have a less harmful net effect in the setting of acute stroke than nonionic LOCM. No comparative data in IV or IA IRCM use in human stroke are available to refute that hypothesis.<sup>3</sup>

Mechanisms contributing to potential differences in IRCM efficacy and safety have been extensively analyzed under a variety of experimental conditions in vitro and in animal models, including coagulation, direct cytotoxic, neurotoxic, osmotic, hydrostatic, and direct vasomotor effects.

**Table 2: Relevant treatment-related variables considered for adjusted analysis**

	Iodixanol	LOCM <sup>a</sup>	P Value
Time to IV therapy (min) (median)	124	115	.25
Onset to puncture (min) (median)	215	205	.29
Proximal MI (vs distal) (%)	45.2	52.0	.51
Thrombolysis only (%)	41.9	36.2	.57
No. microcatheter injections (median)	1	2	.03
Heparin volume (U) (median)	3185	2986.8	.59
New emboli (%)	16.1	11.8	.54
IRCM volume (mL) (median)	85	64	.34
Infarct volume 24 hr (mL) <sup>a</sup> (median)	61.0	50.2	.23

<sup>a</sup> Four LOCM (mOsm/Kg H<sub>2</sub>O): iohexol (672), iopamidol (616), ioversol (651), iopromide (607).<sup>11</sup>

**Table 3: Efficacy and safety outcomes according to iodixanol versus LOCM use**

	Iodixanol (No.) (%)	LOCM (No.) (%)	Absolute % Risk Difference	Relative % Difference
N	31	102	—	—
mTICI 2b/3	16 (51.6)	42 (41.2)	10.4	20.2
mRS 0–2	11 (35.5)	31 (30.4)	5.1	14.4
AICH	9 (29.0)	42 (41.2)	–12.1	–29.6
SICH	2 (6.5)	9 (8.8)	–2.4	–26.1
Mortality	6 (19.4)	26 (25.5)	–6.1	–23.9

**Note:**—AICH indicates asymptomatic ICH.

**Table 4: Relative risk of specified outcomes for iodixanol versus LOCM**

	Unadjusted			Adjusted		
	RR	99% CI		RR	99% CI	
mRS 0–2	1.1675	0.5606	2.4314	1.2002	0.6123	2.3528
mTICI 2b/3	1.2535	0.7291	2.1549	1.2829	0.7888	2.0864
AICH	0.7051	0.3216	1.5457	0.6596	0.3051	1.4260
SICH	0.7312	0.1048	5.1038		NA	
Mortality	0.7593	0.2683	2.1486	0.7538	0.2767	2.0537

**Note:**—RR indicates relative risk; AICH, asymptomatic ICH.

## Coagulation

**Platelet Activity Effects.** Direct activation of platelets (ie, degranulation and release of the procoagulant content of attenuated bodies and  $\alpha$ -granules) is induced in vitro by nonionic LOCM, with no activation by LOCM ionic (eg, ioxaglate) and nonionic dimeric iodixanol.<sup>15-17</sup> Nonionic iohexol and iodixanol are equivalent in reducing platelet aggregation.<sup>18,19</sup> In vitro platelet activation by thrombin is inhibited by ionic LOCM, whereas nonionic monomeric LOCM and dimeric iodixanol did not affect it.<sup>20</sup> Prior antiplatelet use of aspirin conferred neither clinical nor reperfusion benefit nor hemorrhagic risk in conjunction with IV rtPA in the National Institute of Neurological Disorders and Stroke trial, and none has previously been demonstrated in EVT.<sup>21,22</sup> While antiplatelet use in IMS III tended to be associated with increased ICH overall, its use was more common in the iodixanol group, yet ICH was decreased with iodixanol use.

**Thrombin Activity Effects.** The heparin dose used during EVT did not differ between the 2 treatment groups. Nonionic agents cause less direct inhibition of thrombin production compared with ionic IRCM, acting after the generation of thrombin at the step of fibrin monomer polymerization.<sup>23</sup> Both ionic and nonionic agents can prolong clotting time and may exaggerate the effects of anticoagulant and antiplatelet drugs.<sup>24</sup> Nonionic LOCM iopamidol and iohexol have an anticoagulant effect but permit thrombin generation in vitro.<sup>25-27</sup> The anticoagulant effect of iodixanol has been shown to be significantly less than that of iohexol.<sup>16</sup> LOCM iopamidol has been found to have a greater thrombotic effect than iodixanol.<sup>28</sup> One of 3 clinical studies of coronary intervention found a significant decrease in abrupt vessel occlusions with iodixanol, particularly in the absence of glycoprotein IIb/IIIa blockers, while the other 2 found no differences in major cardiac events.<sup>29</sup> No differences in mortality or length of stay were found among 107,994 coronary angiographies or interventions with 3 different LOCM.<sup>29</sup> Outcome differences in IRCM effects between procedures performed for acute occlusive EVT have been suggested for coronary intervention yet have also been inconclusive due to limited power.<sup>30</sup>

**Fibrinolytic Effects.** IRCM delay and impede fibrinolysis by recombinant tissue-type plasminogen activator. In vitro studies have shown that while iohexol delays the onset of lysis induced by all lytic agents, ioxaglate delayed the onset of lysis by rtPA and urokinase but not by streptokinase.<sup>31</sup> In vivo studies in dogs have shown that alteplase-induced fibrinolysis could be inhibited by iohexol. Reocclusion of coronary arteries following fibrinolysis was more common after IRCM administration, despite concomitant aspirin and heparin therapy.<sup>32</sup> Iohexol has been demonstrated to increase plasma levels of tPA plasminogen activator inhibitor type 1 in patients undergoing pulmonary angiography.<sup>33</sup> In an in vitro model of the sonographic effect on fibrinolysis, very limited data suggested that iodixanol may diminish the rate of sonography-assisted thrombus dissolution.<sup>34</sup> While a meta-analysis investigating the fibrinolysis effect of IRCM of any type or route of administration (IV or IA) has suggested no difference in recanalization rates,<sup>35</sup> the wide range of fibrinolytic practices makes the study only marginally relevant to the potential effects of individual IRCM types with EVT of M1 occlusion in

IMS III. Dzialowski et al<sup>3</sup> reported reduced odds of favorable outcome in patients receiving IV contrast for CT angiography before IV thrombolysis.

**Cytotoxic and Osmotic Effects.** Cytotoxic effects on endothelial cells may contribute to thrombosis. While no clinically significant differences among nonionic IRCM are confirmed, buckling of endothelial cells with alteration of function is less conspicuous with iodixanol.<sup>36,37</sup> IRCM can also induce apoptosis of endothelial cells in vitro.<sup>38</sup> Significant in vitro differences between IRCM on red blood cell count morphology may also contribute to thrombosis in vivo, with iodixanol retaining a greater percentage of normal morphology compared with LOCM agents.<sup>39</sup>

Both IV and IA IRCM injection increase the permeability of the blood-brain barrier under normal conditions in animals.<sup>40-42</sup> Osmolality plays an important role in the BBB dysfunction, particularly after ischemic injury, even contributing to larger infarcts with hyperosmolal compared with iso-osmolal IRCM infusion.<sup>12</sup> Hypertension, which may reflexly occur with arterial occlusion, potentiates the effect of these BBB effects.<sup>43</sup> In humans, IRCM identification in the brain or subarachnoid space after aneurysm coiling procedures by using large IRCM volumes is usually asymptomatic.<sup>44,45</sup> Theoretically, it is possible that large IV or IA doses of IRCM (as used in nonischemia EVT procedures) may contribute to exaggerated BBB opening, edema, IRCM deposition, and ICH in ischemic stroke EVT as well.<sup>46,47</sup>

Following acute ischemia in rats, early leakage of MR imaging contrast agents across the BBB has been shown to predict and co-localize to subsequent hemorrhagic transformation.<sup>48,49</sup> In humans, contrast media deposition during MR imaging and CT perfusion in the acute ischemic setting is also a marker of subsequent hemorrhagic transformation.<sup>50-52</sup> Depositions confirmed on both post-EVT CT and MR imaging have also co-localized to MR imaging contrast enhancement and hemorrhagic transformation.<sup>53</sup> MR imaging contrast deposition during routine gadolinium-enhanced MR imaging following IV rtPA occurs in approximately 20% of infarcts and is predictive of subsequent ICH.<sup>54,55</sup> Lummul et al<sup>56</sup> connected CT-hyperattenuated cerebral lesions with IRCM deposition following both CTA/CTP and subsequent EVT. The high incidence of hyperattenuated lesions and the percentage of secondary ICH suggest that they both may be IRCM-volume related. It remains unclear whether contrast media deposition is both effect and cause, with IRCM leaking across the BBB contributing to additive cytotoxic effects on the interstitium and neuronal elements. However, in IMS III, the median iodixanol volume was numerically higher than that for LOCM, suggesting that either worse measured outcome differences were not merely LOCM-volume-related or greater iodixanol volume exerted a protective effect.

Complex mechanisms beyond osmolality-related toxicity and dysfunction may be operative.<sup>57,58</sup> Heinrich et al<sup>59</sup> compared the cytotoxic effects of dimeric iso-osmolal IRCM (iodixanol, iotrolan) and iso-osmolal formulations of monomeric IRCM on renal tubular cells in vitro and found that dimeric IRCM have stronger cytotoxic effects, postulating a mechanism beyond osmolality alone. Molecular chemotoxicity decreases as the number of carboxyl groups decreases and the number of hydroxyl groups increases, and IRCM with no carboxyl groups and a number of

hydroxyl groups evenly distributed around the main molecule have reduced neurotoxicity.<sup>60,61</sup> Iodixanol has an increased number of hydroxyl groups ( $n = 9$ ) compared with LOCM (eg, 5 for iopamidol), but more carboxy groups (6 versus 3), theoretically disadvantageous in human use. Increasing the number of hydroxyl groups also increases solubility, thus reducing the tendency to bind to tissues and proteins, which may then lead to inhibition of enzyme systems, including acetylcholinesterase.<sup>62,63</sup> The net vector for the benefit of the complex structural arrangement of iodixanol is uncertain.

Hyperosmolality-toxicity injury may be offset, in part, by a beneficial osmotic tonicity effect of intravascular IRCM on the intravascular and extracellular spaces based on molecular size. Dimeric iodixanol (1000 Da) is approximately twice as large as monomeric iopamidol (550 Da). Five times larger than mannitol (182 Da), iodixanol may not only be less able to traverse early damage to the BBB to exert adverse direct toxic or osmotic effects beyond endothelial cell tight junctions in the basal lamina or in the extracellular space, but it also may offer a microvascular osmotic advantage.<sup>64</sup> Conversely, monomeric LOCM may ultimately more easily traverse the damaged membrane to promote increased edema by an osmotic tissue effect. While conflicting evidence regarding increased neurotoxicity once the IRCM has crossed the BBB in animals and humans exists,<sup>12,14,65-68</sup> an additive effect of IRCM traversing the damaged BBB into the interstitium, affecting cellular and neural elements, contributing to greater ICH potential and neural injury, is hypothesized.

**Hydrostatic Effects.** Viscosity differences (iodixanol 11.8 cP at 37° versus iopamidol 4.7 cP) may simultaneously lead to a reduced hydrostatic effect of viscous, dimeric iodixanol, with prolonged vascular retention at the injured BBB, and may contribute to the reduced infarct edema volume measured in rats.<sup>69</sup> Hydrolysis of iodixanol *in vitro* can produce a derivative of propylene glycol (2,3-dihydroxy-1-propylamine HOCH<sub>2</sub>-CH [OH]-CH<sub>2</sub>-NH<sub>2</sub>), which, when injected intra-arterially in a rat ischemia model, has been found to decrease BBB dysfunction by a “sealing” effect, with subsequent decreased permeability and infarct size.<sup>70</sup> Similar hydrostatic IA “sealing” effects on the BBB could even be possible under certain conditions.<sup>71,72</sup> Molecule size alone may present a relative microvascular seal, delaying not only early ionic edema but also diminishing later vasogenic edema associated with hemorrhagic transformation.

Relatively reduced asymptomatic ICH and SICH with iodixanol in IMS III, despite the possibility of better mTICI reperfusion and larger infarct volume, contradict the theoretic construct of reperfusion ICH effects, suggesting that iodixanol may somehow offer an unrelated protective effect against ICH.<sup>73</sup> The mechanism of hemorrhagic transformation, though linked to reperfusion, infarct volume, and edema, might have a separate and different pathophysiologic pathway after reperfusion of acute ischemic stroke in humans and animals.<sup>74,75</sup> Infarct size and ICH differences are greater in rats with temporary-versus-permanent MCA occlusion.<sup>76</sup> Reduced infarct edema volume as a measure of reduced reperfusion injury with both LOCM-versus-saline reperfusion and viscous iso-osmolal-versus-less viscous LOCM has been found in rats.<sup>1,2</sup> In humans, improved mTICI reperfusion following ischemia would be anticipated to increase levels of

active oxygen species, including superoxide radical and nitric oxide.<sup>77,78</sup> Oxidative radicals trigger activation of metalloproteinases, which, in turn, potentiate injury to microvasculature and neural cells.<sup>79,80</sup> However, IRCM may decrease the endothelial production of nitric oxide by reducing the activity of the enzyme nitric oxide synthase, which is responsible for the endogenous synthesis of this vasodilator.<sup>81,82</sup> Variable vasoactive effects of IRCM have been identified in the renal vasculature, where both iopamidol and iodixanol caused a brief initial vasodilation, followed by increased resistance with iopamidol, but not iodixanol.<sup>83</sup> Increased CO<sub>2</sub> release from the rat hippocampus incubated with the iso-osmolar dimers iotrolan and iodixanol has been measured, a potentiator of vasodilation. Increased CO<sub>2</sub> production could involve an effect of the glucose metabolic pathway or be indirect via an unspecified mechanism that increases cell glucose use.<sup>84</sup> Potential glucose metabolism effects of IRCM have been identified *in vitro* and *in vivo* for metrizamide, but not for iohexol or iopamidol. Clinically significant vasomotor differences in the cerebral vasculature in humans are unknown.

**Miscellaneous Effects.** IRCM have been reported to adversely affect oxyhemoglobin dissociation.<sup>85</sup> Decreased pH or increased temperature in the hypoxic brain tissue can cause changes in the physicochemical properties of IRCM as well. Increased BBB disruption has been demonstrated in rabbits with IA injection of higher iodine-concentration IRCM (300 versus 150 mg/mL), at a lower temperature (24°C versus 37°C), during a briefer time (1 versus 30 seconds).<sup>86</sup> The role that these miscellaneous effects might play in EVT can only be theorized.

ICH has been previously linked to microcatheter IRCM injections during EVT.<sup>67,87</sup> Microcatheter IRCM injections push saline ahead at higher initial pressures and flow rates, which decrease as the catheter becomes IRCM-filled (D. Hansmann, EKOS, unpublished data, 2014). The viscosity of iodixanol may diminish such distal catheter pressure and flow effects compared with LOCM, and it offers a relative safety margin reflected in lower ICH and SICH rates. Microcatheter IRCM injection delivers a higher concentration of IRCM locally within the occlusion, which then may wash out more slowly from patent or partially obstructed microvasculature, thereby amplifying protective hydrostatic microvascular iodixanol effects. Local microcatheter saline injections, used to clear catheters of IRCM, with pressure and flow increasing through the act of clearance, may be equally responsible for any untoward effects of IRCM MCI.

There are limitations to our results, analysis, and hypotheses. First, the importance of an unrecognized baseline or treatment factor may be underestimated. Prior antiplatelet and iodixanol use may favor revascularization and clinical outcomes in a way not previously demonstrated in IV or EVT revascularization studies. The specifics of recording IA injections of IRCM in a revascularization procedure leave room for wide ranges of practice variables that theoretically may have a secondary effect on outcome. Injections such as hand or power, intracranial microcatheter or cervical guide, saline-diluted or full-strength, high- or low-pressure, large- or low-volume may all be performed during the same procedure. Differences among operators that almost assuredly exist in all these variables may become relatively reproducible

within a the practice of a single operator or center. Site variables, then, might affect outcomes.

LOCM use following IV rtPA may not have the same effects by comparison in the absence of IV rtPA. While the impact of any proved, actionable differences between IRCM may be diminished in the current EVT atmosphere of shorter procedures with reduced IRCM volume use with application of devices not studied in IMS III, the use of MCI with LOCM may still prove to be a relevant risk factor.

While this is an analysis of a homogeneous population of M1 occlusion, new emboli during treatment in previously uninvolved vessels occurred in 12.8% of subjects with M1 occlusion in IMS III, numerically more common in the iodixanol group (16.1% versus 11.8%). An estimated 13% difference in mRS 0–2 outcomes between subjects with and without new emboli in IMS III has been reported.<sup>4</sup> While new emboli may have contributed to nonsignificantly larger infarcts in the iodixanol group, it remains unclear how larger infarcts relate to better clinical outcome.

## CONCLUSIONS

A potential protective effect of iodixanol use in the EVT of M1 occlusion is proposed in IMS III, but perhaps only in the setting of MCI. Iodixanol contributes less endothelial cytotoxic effect to the thrombotic process. Its lower anticoagulant effect may diminish hemorrhagic transformation, with numerically fewer SICHs and fewer asymptomatic ICHs despite greater prior antiplatelet use. Its passage across the BBB is less than that with LOCM, while retaining a favorable osmotic microvascular potential. It may also have beneficial hydrostatic and vasoactive activity. The hypothesis that a small difference in outcomes may indeed exist by using different IRCM remains unproven in a small study population with only 50% of subjects with major arterial occlusion predisposed to good outcome.<sup>88</sup> Further analysis of not only the magnitude of the clinical effect potential of isosmolal IRCM but also the mechanisms conferring such benefit is warranted.

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